

# Topical Uses of Vitamin C

Several studies exist in the literature to show that topical and oral vitamin C is effective in treating photodamaged skin, rejuvenation, pigmentation disorders and photoprotection. In this article, we'll review the mechanism of action of vitamin C and discuss its clinical uses in dermatology.

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## Mechanism of Action

Reactive oxygen species (ROS) are an inherent part of the anabolism and catabolism of tissues, including skin. Most oxygen in the body is used in cellular metabolism. Through a series of 1-electron subtractions, molecular oxygen is in sequence changed to superoxide anion, hydrogen peroxide, hydroxyl radical, and finally, to water. Most reactions occur in mitochondria and are related to energy production. Cellular enzymes and metabolic processes ordinarily keep oxidative damage to cells at minimum. In times of increased oxidative stress, however, including high metabolic demands and outside forces such as sunlight, smoking and pollution, protective controls may not be adequate and oxidative damage may occur. The most damage occurs from free radicals.

Free radicals are defined as atoms or molecules with an unpaired electron; examples include superoxide anion, peroxy radical and hydroxyl radical. These molecules are extremely chemically reactive and short-lived; they react at the place where they are created. Other reactive molecules such as molecular oxygen, singlet oxygen and hydrogen peroxide are not free radicals per se, but are capable of initiating oxidative reactions and generating free radical species. Together these free radicals and reactive oxygen molecules are called ROS.<sup>5</sup>

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Antioxidants are unstable compounds: this allows them to function in redox reactions. Instability makes them difficult to formulate in an acceptable, stable composition for cosmetic use. This why products that are commercially available should have the support of clinical trials and manufactured with tight quality control.

Low molecular weight antioxidants include L-ascorbic acid (vitamin C) in the fluid phase, glutathione in the cellular compartment, vitamin E in membranes and ubiquinol in mitochondria.<sup>5</sup>

Antioxidants can be supplied to skin through fast diet and oral supplementation. Physiologic process related to absorption, solubility and transport limit the amount that can be delivered into the skin. Direct application has added advantage of targeting the antioxidants to the area of the skin needing the protection. Based on in vitro studies, vitamin C should be formulated at pH levels less than 3.5 to enter the skin. Tissue levels are saturated after three daily applications; the half-life of tissue disappearance is about 4 days.<sup>6</sup>

In the skin, ascorbic acid acts as an antioxidant by scavenging and quenching free radicals (protects the aqueous environment) and by regenerating vitamin E from its radical form. After loss of a second electron, the resulting oxidation product dehydroascorbic acid can be regenerated by dehydroascorbic acid reductase, or as frequently happens, may decay as the lactone ring irreversibly opens.<sup>5</sup>

Vitamin C may also act as a pro-oxidant in the presence of transitional metal ions, such as iron.<sup>7</sup> L-ascorbic acid is essential for collagen biosynthesis; it serves as a cofactor for proline and lysine hydroxylases, enzymes necessary for molecular stability and intermolecular cross-linking, respectively.<sup>8</sup>

It has been reported that vitamin C regulates collagen synthesis and production<sup>9</sup> as it stimulates type I procollagen synthesis in cultured human skin fibroblasts.<sup>10,11</sup>

L-ascorbic acid may inhibit elastin biosynthesis<sup>12</sup> and could therefore, be useful for reducing the increased elastin accumulation that occurs in photoaged skin.<sup>13</sup>

## Animal Studies

Darr et al, demonstrated that topical L-ascorbic acid protected porcine skin from UVB and UVA phototoxic injury as measured by erythema and sunburn cell formation.<sup>14</sup>

Lin et al, performed a study in pig skin. They applied aqueous solution of 15% L-ascorbic acid alone and in combination with  $\alpha$ -tocopherol. They observed that vitamin C has an antioxidant and photoprotection effect if used alone or in combination with vitamin E. They suggest that vitamin C may protect against skin cancer and photoaging.<sup>15</sup>

New findings in mouse skin regarding the absorption of vitamin C (MAP) after ablation procedures have been reported. The Er:YAG laser enhanced the deposition ratio to 123.22-fold in contrast to intact skin. Microderma-brasion-treated skin was approximately 20-fold higher than that across intact skin.<sup>16</sup>

## In vitro Studies

Regarding collagen production, Dumas et al, showed that L-ascorbic acid stimulates the production of collagen I and III in human dermal fibroblasts. Researchers performed the study in UV-exposed and non-exposed cutaneous sites of 19 to 70 year old patients.<sup>11</sup>

Tajima et al, demonstrated that vitamin C enhances the transcription of type I and III collagen genes.<sup>9</sup> Vitamin C also has a photoprotector effect. It has been reported that this antioxidant molecule protects against direct cell death and protein oxidation after UVA, UVB and UVA+B irradiation.<sup>17</sup>

Leveque et al, did a study in which they evaluated the effect of topical 8% L-ascorbic acid in human skin fragments. Results were assessed by gas chromatography mass spectrometry. They observed that a high concentration remained constant if it was applied every 8 hours, and also found that it has a major photoprotectant effect.<sup>18</sup>

Recently, it has been published that in the absence of co-antioxidants, vitamin C combined with UV exposure and iron ions may together cause stratum corneum lipid damage. It is important to emphasize that researchers used 100 mM. In this same study, in other keratinocyte models, they observed that ascorbic acid was able to lower the intracellular peroxide content in a concentration-dependent manner.<sup>19</sup>

## Clinical Studies

There are various cosmetic products<sup>20-23</sup> available in the United States that contain different forms of vitamin C; however, the data presented only applies to products for which there is supporting published literature. These products contain L-ascorbic acid as an active ingredient and differ only in the vehicle in which they are contained.

Vitamin C has a beneficial effect in photodamaged and aged skin. With increasing age, the number of papillae in the epidermal-dermal junction zone in human skin is reduced. It has been reported that with the use of 3% ascorbic acid there is a significant increase in the density and number of dermal papillae. This may explain the therapeutic effect for partial corrections of structural changes associated with the aging process.<sup>24,25</sup>

Humbert et al, performed a double-blind, randomized study in which they compared vitamin C 5% cream to placebo. Applying the cream daily for 6 months, they observed a statistically significant improvement of hydration, wrinkles, glare and brown spots in the vitamin C 5% group. Analysis of the skin replicas showed that, compared with placebo, there exists a highly significant increase in the density of skin microrelief as well as decrease of deep furrows with the vitamin C over a 6 month period.<sup>20</sup>

A statistically significant improvement is reported in photoaged skin with the use of 10% ascorbic acid. Biopsies in a study by Fitzpatrick and Rostan showed an increase in Grenz zone collagen and collagen type I.<sup>26</sup>

Another author reports the efficacy of L-ascorbic acid in photodamage facial skin. Traikovich demonstrated statistically significant improvement in 84.2% of the treated patients over placebo patients.<sup>21</sup>

Vitamin C it has also been reported as an effective treatment for melasma. Espinal-Perez et al, performed a study in patients with melasma in Mexico using 5% ascorbic acid versus 4% hydroquinone. They observed that the best subjective improvement was in the hydroquinone group, however colorimetric measures showed no statistical difference. Subjects treated with ascorbic acid and hydroquinone had side effects in 6.5% and 68% respectively; the most common side effects were redness and irritation.<sup>22</sup>

Besides vitamin C uses in photorejuvenation and melasma, Ikeno et al, performed a study in patients with facial acne vulgaris. They compared topical vitamin C 5% to topical clindamycin 1% (Cleocin). The patients in the vitamin C group showed improvement 75% (28/37) compared with 54.5% (18/33) in the Clindamycin group. Means percentage reductions in inflammatory and non-inflammatory lesion counts were statistically significant in the vitamin C treatment group compared with the Clindamycin treatment group ( $P \leq 0.01$  and  $P \leq 0.05$ , respectively).<sup>27</sup>

## Combination Pharmaceutical Studies

The combination of vitamin C with topical retinoids for rejuvenation and treatment of photodamaged skin has been studied. Rachel et al, found that the combination of trichloroacetic acid peels, 0.05% tretinoin and ascorbic acid lotion are more effective than any of the components alone. In this study, they found histological changes such as thicker epidermis, decreased melanocyte hypertrophy and compactation of the basket-weave pattern of the stratum corneum. The skin of these patients was from the postauricular area, skin that does not undergo similar chronic exposure as the face.<sup>28</sup>

Recently, it has been reported that the combination of vitamin C with retinol is able to reverse, at least in

part, skin changes, induced by both chronological aging and photoaging. Seite et al, performed two double-blind studies in aged and photoaged skin. Subjects applied this combination daily for 3- and 6-month periods. They found histological differences from baseline in both groups, such as reduction in type III collagen and thickening of the epidermis.<sup>23</sup>

It has been reported, that long-term oral administration of ascorbic acid and a-tocopherol significantly reduced the sunburn reaction to UVB radiation, and significantly less thymine dimmers were induced, suggesting that antioxidant treatment may protect against DNA damage of the skin. <sup>29</sup>

## Vitamin C and Our Patients

Vitamin C has been used for the treatment of several dermatological conditions (photodamage skin, rejuvenation, pigmentation disorders and photoprotection) however, only a few articles <sup>20-23</sup> are comparative and show results in humans.

A very important study made in the mouse, suggests that the Er:YAG laser, when used before applying vitamin C, improves the flux and absorption of the ascorbic acid in the skin. These findings suggest that skin resurfacing induced by laser can have some clinical applications in the future.

Oral supplementation prevents the oxidative stress induced by sunburn<sup>28</sup> and this finding suggests that oral vitamin C intake could be useful. However, we need to know all the metabolic pathways and specific actions of this vitamin.

The biochemical effect of the ascorbic acid is related to the transformation of procollagen into collagen<sup>1</sup>. We hypothesized that the UVA and UVB radiation could have two effects; one, related to the biochemical transformation of the ascorbic acid molecule and this transformation do not allow that ascorbic acid act as a normal coenzyme; and the other effect is that probably the gene which produces procollagen protein is damaged and this even though there is ascorbic acid as coenzyme it does not act because there is no procollagen.

We may suggest that the benefit of using vitamin C by topical route only can be effective if we do not have damage of the gene that produces procollagen. In addition, it is reasonable to recommend sun protection measures, sunscreens for prevention of photodamage, and topical vitamin C to improve photodamage to our patients.

### Sidebar 1:

## Vitamin C (Ascorbic acid)

A vitamin is defined as an organic compound that is required in the diet in small amounts for the maintenance of normal metabolic integrity. Vitamin deficiency causes a specific disease, which is cured or prevented only by restoring the vitamin to the diet.<sup>1</sup>

Vitamin C in the active form is called L-ascorbic acid and is present as ascorbate, a water-soluble molecule, in most biologic settings. It's present in citrus fruits, berries, melons, tomatoes, green peppers, raw cabbage and leafy green vegetables. It is not synthesized by the body. Vitamin C is the most important antioxidant in extracellular fluids and in many cellular activities.<sup>2</sup>

Vitamin C is a vitamin for human beings and other primates, the guinea pig, bats, passerine birds, and most fishes and invertebrates; other animals synthesize it as an intermediate in the uronic acid pathway of glucose metabolism. In those species for which it is a vitamin, there is a block in the uronic acid pathway due to absence of gulonolactone oxidase. Both ascorbic acid and dehydroascorbic acid have vitamin activity. Dehydroascorbic acid is generated spontaneously from vitamin C by oxidation in the air.<sup>1</sup> Signs of vitamin C deficiency in scurvy include skin changes, fragility of blood capillaries, gum decay, tooth loss, and bone fracture, many of which can be attributed to deficient collagen synthesis.<sup>4</sup>

Sidebar 2:

## Vitamin C: The Co-enzyme for Two Groups of Hydroxylases

Ascorbic acid has specific roles in the copper-containing hydroxylases and the  $\alpha$ -ketoglutarate-linked iron-containing hydroxylases. It also increases the activity of a number of other enzymes in vitro, though this is a nonspecific reducing action. In addition, it has a number of nonenzymatic effects due to its action as a reducing agent and oxygen radical quencher. A number of iron-containing, ascorbate-requiring hydroxylases share a common reaction mechanism in which hydroxylation of the substrate is linked to decarboxylation of  $\alpha$ -ketoglutarate. Vitamin C enhances the intestinal absorption of iron and the mobilization of iron from tissue depositories.

Many of these enzymes are involved in the modification of precursor proteins. Proline and lysine hydroxylases are required for the postsynthetic modification of procollagen to collagen, and proline hydroxylase is also required in formation of osteocalcin and the C1q component of complement. Aspartate b-hydroxylase is required for the postsynthetic modification of the precursor of protein C, the vitamin K-dependent protease that hydrolyzes activated factor V in the blood clotting cascade. Trimethyllysine and -butyrobetaine hydroxylases are required for the synthesis of carnitine.<sup>1</sup>

Recently, formulators made esterified derivatives from L-ascorbic acid, these derivatives are ascorbyl-6-palmitate and magnesium ascorbyl phosphate (MAP) which are more stable.<sup>3</sup>